



Effects of Olanzapine versus Risperidone on Thyroid Function in Schizophrenic Patients

KEYWORDS

Schizophrenia, olanzapine, Risperidone, thyroid function tests.

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ABSTRACT

Background: Thyroid function abnormalities are relatively common in patients with psychiatric diseases especially schizophrenia, but it remains unknown if these are related to a genetic predisposition or to antipsychotic treatment.

Aim: The aim of this study was to evaluate the effects of atypical antipsychotic, olanzapine and risperidone on thyroid function in a group of newly diagnosed schizophrenic patients.

Method: A non-randomized design was used in this study. Subjects were recruited from an urban community mental health clinic at AL-Salam Teaching Hospital. Sixty-nine (69) patients meeting the criteria for a diagnosis of schizophrenic disorder were assigned to monotherapy with olanzapine (n=36), or risperidone (n=33). Forty (40) apparently healthy volunteers matched in age, sex and body mass index (BMI) to the patients were collected as a control group. Total triiodothyronin (tT3), total thyroxin (tT4) and thyroid stimulating hormone (TSH) were evaluated. Analysis of variance and Student's t-test were used in the statistical analysis.

Results: Total triiodothyronin (tT3) concentrations for control, olanzapine and risperidone groups before treatment were 1.00 ± 0.20 , 1.14 ± 0.34 , and 1.11 ± 0.25 respectively, total thyroxin (tT4) were 7.04 ± 1.21 , 7.18 ± 1.72 and 7.38 ± 1.72 respectively and thyroid stimulating hormone (TSH) values were 1.26 ± 0.69 , 1.66 ± 1.13 and 1.42 ± 0.69 respectively. Olanzapine treatment for 8 weeks significantly decreases serum levels of tT4 at week 4 and week 8 of therapy 6.46 ± 1.42 and 6.44 ± 1.96 respectively, in contrast TSH serum levels significantly increased at week 4 and week 8 of olanzapine therapy 1.70 ± 1.02 and 2.11 ± 1.28 respectively. Therapy with risperidone only significantly increased serum levels of TSH at week 4 and week 8 of therapy 1.71 ± 0.67 and 1.90 ± 1.11 respectively.

Conclusions: Alteration in the levels of thyroid hormones can occur in schizophrenic patients during therapy. Although routine monitoring of thyroid function in olanzapine and risperidone treated schizophrenic patients is not recommended, attention should be paid to thyroid function in such patients.

Introduction

Schizophrenia is one of the most severe psychiatric disorders with an estimated prevalence of 0.7–1.0% in the population worldwide. It often runs a chronic and debilitating course, with many patients responding poorly to medication and suffering frequent and disrupting relapses (MacDonald and Schulz, 2009).

The abnormalities of thyroid function in schizophrenic patients were first documented in scientific studies over the past 40 years in chronic patients treated with antipsychotic medications (Kline et al., 1968).

Dopamine that is released inside the body is known to inhibit the stimulatory effects of thyroid-releasing hormone, and any drug with dopaminergic activity can inhibit thyroid stimulating hormone (TSH) secretion (Singer, 1986). Thus, treatment of patients with conventional antipsychotics may lead to abnormal thyroid test results based on drugs' pharmacologic profile and dopaminergic activity (Jefferson, 1988).

Clozapine as compared with haloperidol and control groups has demonstrated a decreased TSH response, most likely relating to its different pharmacologic profile and different dopaminergic actions (Paunovic et al., 1991).

The commonly used antipsychotic haloperidol can enhance type 2 deiodinase, while clozapine decreases type 2 but increases type 3 deiodinase activities in several brain regions (Eravci et al., 2000). In addition, some antipsychotics, such as clozapine, are piperazine-containing drugs that undergo N-glucuronidation. Given that the enzyme UDP-glucuronosyltransferase (UGT) is responsible for the glucuronidation of

TH and of certain psychotropic medications (De Leon, 2003); a competitive mechanism may be conducive to TH level changes (Kelly and Conley, 2005).

Finally, even in cases where no change in circulating levels of TH is observed, deregulated deiodinase activity may affect distribution and local regulation of TH (Armstrong et al., 1999).

We conducted a prospective therapeutic clinical trial to compare the effects of second generation antipsychotic olanzapine and risperidone on thyroid function during 4 and 8 weeks of treatment with these drugs in newly diagnosed schizophrenic patients.

Method

Patients and Control Subjects

Sixty-nine patients fulfilling Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV 1994) diagnostic criteria for schizophrenia were included in this study. Thirty six (52.2%) (25 male and 11 female) of the patients were on stable dosage of olanzapine (ranged from 5 to 20 mg/d), thirty three (47.8%) (22 male and 11 female) were on risperidone (ranged from 4 to 12 mg/d), the drugs were dosed according to standard dosage procedures. The observation period was 8 weeks on 3 steps (baseline, after 4 weeks and after 8 weeks).

All patients gave written informed consent to participate in this study, which was performed according to the guidelines of the Ethical Committee of the Medical Faculty of Ministry of Health.

Patients were excluded on the basis of current substance abuse; diabetes mellitus; thyroid disease; pregnancy; other medical illness including severe cardiovascular, hepatic, or renal disease; or unstable psychiatric illness, and those receiving any drug therapy. Forty apparently healthy volunteers without previous history of any psychiatric disorder were recruited as a control group with approximately age, sex and BMI matching to the patient groups.

Study protocol and Outcome measures

This was an 8 weeks therapeutic clinical trial of treatment with olanzapine or risperidone in newly diagnosed or drug free (for at least 4 weeks) schizophrenic patients divided into two groups. Measures at baseline, after 28 (4 weeks) and then after 54 (8 weeks) days of drug treatment included Thyroid stimulating hormone (TSH), total triiodothyronin (tT3), and total thyroxin (tT4).

Blood was drawn in the morning from an antecubital vein into test tubes. Serum was separated from erythrocytes by centrifugation at 3000 rpm for 10 minutes at 4°C (39°F) immediately after collection. Serum samples were stored frozen at -80°C (-18°F) until assayed.

Serum thyroid stimulating hormone (TSH) µIU/ml, total triiodothyronin (tT3) ng/ml, and total thyroxin (tT4) µg/dl concentrations were assayed by the Microplate Enzyme Immunoassay (ELISA) using Accu-Bind kits, USA.

The same measures were applied to the control group which is the third group.

Statistical Analysis

Descriptive data given are mean values. A paired t test was used for within-group comparisons (week 4 vs. baseline, week 8 vs. baseline and week 4 vs. week 8). Differences between groups of patients with regard to the prescribed antipsychotic agent were assessed using one-way ANOVA with post-hoc Waller Duncan test, as appropriate. A t test for independent samples (unpaired) was performed for between-group comparisons with respect to changes (in all investigated parameters) between baseline and control. Values are expressed as mean (±SD) unless otherwise stated.

Statistical significance was accepted at a 2-tailed p value smaller or equal to 0.05 (p<0.05). Statistical analyses were calculated using SPSS (Statistical Package for Social Sciences) release 14 for Windows.

Results

Sixty-nine newly diagnosed schizophrenic patients were included in this study, divided into two groups. Olanzapine-treated group includes 36 patients (25 males and 11 females) and risperidone-treated group includes 33 patients (22 males and 11 females). A group of 40 healthy volunteers with approximately age, sex and BMI matching to the patients was taken as control group. The characteristic variables of number, age, weight, and sex for patients in drug treatment groups and for subjects in control group was shown in (Table 1). All subjects were studied at baseline, after 4 weeks and after 8 weeks of treatment. All patients and subjects had all 3 thyroid function tests completed at baseline, after 4 weeks and after 8 weeks of study.

There were no statistically significant differences between groups in the baseline levels of TSH, tT3 and tT4 as shown in (Table 2).

In olanzapine-treated group, no significant changes were found in tT3 levels at any study point in comparison with the baseline levels and with the control group as shown in (Table 3), whereas significant changes had occurred in tT4 levels with a mean decrease of 0.71 µg/dl ± 1.75 after 4 weeks and 0.73 µg/dl ± 1.92 after 8 weeks of treatment as shown (Table 4), TSH also shown significant changes only at week 8

of treatment with a main increase of 0.44 µIU/ml ± 0.77 when compared with baseline levels and control group, no significant changes were found in TSH levels at week 4 of treatment as shown in (Table 5).

In risperidone-treated group, no significant changes were found in tT3 and tT4 levels at any study point in comparison with the baseline level and with the control group as shown in table 3 and 4 while TSH shown significant changes with mean increase of 0.28 µIU/ml ± 0.41 at week 4 and 0.48 µIU/ml ± 0.97 at week 8 of treatment when compared with baseline levels and control group as shown in (Table 5).

Table 1 : Characteristics of patients and control and drug treatment.

Variables	Olanzapine (mean ± SD)	Risperidone (mean ± SD)	Control (mean ± SD)	P-value
Number	36	33	40	
Age (year)	33.51±8.16	31.37±7.99	30.9±6.42	0.8
Weight (Kg)	67.90±7.09	70.81±8.9	68.22±5.82	0.2
Sex (male/female)	25/11	22/11	27/13	

Table 2 : difference in mean±SD of baseline variables between olanzapine, risperidone and control.

Variables	Olanzapine n=36 Mean± SD	Risperidone n=33 Mean± SD	Control n=40 Mean± SD	P-value
tT3 (ng/ml)	1.14±0.34	1.11±0.25	1.00±0.20	0.06
tT4 (µg/dl)	7.18±1.72	7.38±1.62	7.04±1.21	0.6
TSH (µIU/ml)	1.66±1.13	1.42±0.69	1.26±0.69	0.1

Table 3 : tT₃ effects of olanzapine and risperidone among schizophrenic patients and in comparison with control group.

Variable	Olanzapine n=36 Control n=40 (mean±SD)		Risperidone n=33 Control n=40 (mean±SD)	
	Control	Mean±SD	Control	Mean±SD
tT3 (ng/ml)	Control	1.00±0.20	Control	1.00±0.20
	Baseline	1.14±0.34	Baseline [¶]	1.11±0.25
	Week 4*	1.10 ± 0.30	Week 4 [¶]	1.12 ± 0.25
	Week 8*	1.26 ± 0.38	Week 8 [¶]	1.11 ± 0.25

*: Significantly not different (p=> 0.05).

¶: Significantly not different (p= >0.05).

Table 4 : tT₄ effects of olanzapine and risperidone among schizophrenic patients and in comparison with control group.

Variable	Olanzapine n=36 Control n=40 (mean±SD)		Risperidone n=33 Control n=40 (mean±SD)	
	Control	Mean±SD	Control	Mean±SD
tT4 (µg/dl)	Control	7.04 ± 1.21	Control	7.04 ± 1.21
	Baseline	7.18 ± 1.72	Baseline	7.38 ± 1.62
	Week 4*	6.46 ± 1.42	Week 4	7.32 ± 1.47
	Week 8**	6.44 ± 1.56	Week 8	7.27 ± 1.80

*: Significantly different from the baseline (p= 0.02).

** : Significantly different from the baseline (p= 0.03).

¶: Significantly not different from week 4 (p= 0.12).

: Significantly not different ($p = >0.05$).

Table 5 : TSH effects of olanzapine and risperidone among schizophrenic patients and in comparison with control group.

Variable	Olanzapine n=36 Control n=40 (mean±SD)		Risperidone n=33 Control n=40 (mean±SD)	
	TSH (µIU/ml)	Control	1.26 ± 0.69	Control
Baseline		1.66 ± 1.13	Baseline	1.42 ± 0.69
Week 4 *		1.7 ± 1.02	Week 4 ^{ns}	1.71 ± 0.67
Week 8**		2.11 ± 1.28	Week 8 ^{ns, ns}	1.9 ± 1.11

*: Significantly not different from the baseline ($p = 0.7$).

** : Significantly different from the baseline ($p = <0.002$).

** : Significantly different from week 4 ($p = <0.001$).

^{ns}: Significantly different from the baseline ($p = <0.001$).

^{ns, ns}: Significantly different from the baseline ($p = <0.01$).

: Significantly not different from week 4 ($p = <0.2$).

Discussion

Thyroid dysfunction is relatively common in patients with schizophrenia, possibly related to a genetic linkage of the disorders and to antipsychotic treatment (Kelly and Conley, 2005). Many drugs can interfere with biochemical tests of thyroid functions by interfering with the synthesis, transport, and metabolism of thyroid hormones, or by altering the synthesis and secretion of thyrotrophin (TSH) (Kundra and Burman, 2012). In most cases, patients with abnormal thyroid function tests were found to be clinically euthyroid (Sim *et al.*, 2002), only rarely, however, do these effects causes overt, clinically apparent thyroid disease (Gittoes and Franklyn, 1995).

In this study, at baseline, no patients were found to have abnormal values for thyroid function test parameters. This is in agreement with Kelly and Conley, 2005 as they reported that schizophrenic patients at baseline have no significant differences in thyroid function test parameters. While in contrast Sim *et al.*, 2002 reported a percentage as high as 36% of all patients with chronic hospitalization for schizophrenia had abnormal thyroid function tests.

The present study also reported a significant reduction in total thyroxin level (tT4) in schizophrenic patients after 4 and 8 weeks of continuous olanzapine therapy, with a significant elevation in TSH levels after 8 weeks of therapy. While patients on risperidone therapy showed a significant elevation in serum TSH levels after 4 and 8 weeks of continuous therapy.

Few data were available concerning the effects of antipsychotic drugs on thyroid function. Fluctuations in serum levels of thyroid hormones have been reported with both typical antipsychotic drugs (Baumgartner *et al.*, 2000), and atypical antipsychotic drugs (Grunder *et al.*, 1999).

Paunovic *et al.*, 1991 reported that clozapine (an atypical antipsychotic), resulted in an elevation in free thyroxin level and that 0.4% of the patients treated with this drug in the clinical trial had an elevated serum TSH levels. Rarely, hyperthyroidism and goiter have also been reported in trials during quetiapine and olanzapine therapy (Physician's Desk Reference, 56th ed. Montvale. NJ: Medical Economics Co. Inc; 2003).

A possible explanation to our finding with olanzapine is that, antipsychotics such as clozapine, loxapine, chlorpromazine, and olanzapine are all piperazine-containing drugs that undergo N-glucuronidation by UGT1A4 (Chin and Huskey, 1998).

In the past 10 years, it becomes oriented that many agents do compete for the glucuronidation of olanzapine representing a possibility for drug interactions through this pathway (Linnet, 2002).

Additionally, the enhanced elimination of thyroid hormones through the phase 2 UGT enzyme system may be the mechanism responsible for increasing serum TSH levels (Vansell and Klaassen, 2002).

It is also known that endogenous dopamine inhibit the stimulatory effects of thyroid releasing hormone and any drug with dopaminergic activity can inhibit TSH secretion (Singer, 1986).

Thus, it is not surprising that patients treated with antipsychotics will experience abnormal thyroid tests on the basis of the drugs pharmacologic profile and antidopaminergic activity (Jefferson, 1988).

Regarding risperidone and in contrast to this study result, Kelly and Conley, 2005 reported that risperidone causes no significant effects on parameters of thyroid function tests.

Conclusion

Alteration in the levels of thyroid hormones can occur during therapy with antipsychotic drugs. Although routine monitoring of thyroid function in olanzapine- and risperidone-treated schizophrenic patients is not recommended, attention should be paid to thyroid function in such patients.

REFERENCE

- American Psychiatric Association, (1994). Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), fourth ed. America Psychiatric Association Publications Division, Washington, DC, pp. 273-289.
- Armstrong, N.M., Huang, H., Remo, B.F., Liu, T.T., & Brown, D.D. (1999). Asymmetric growth and development of the *Xenopus laevis* retina during metamorphosis is controlled by type III deiodinase. *Neuron*, 24: 871-878.
- Baumgartner, A., Pietzcker, A., & Gaebel, W. (2000). The hypothalamic-pituitary-thyroid axis in patients with schizophrenia. *Schizophr Res*; 44: 233-243.
- Chiu, S.H.L., & Huskey, S.E.W. (1998). Species differences in N-glucuronidation. *Drug Metab Dispos*; 26: 838-847.
- De Leon, J. (2003). Glucuronidation enzymes, genes and psychiatry. *Int J Neuropsychopharmacol*; 6: 57-72.
- Eravci, M., Pinna, G., Meinhold, H., & Baumgartner, A. (2000). Effects of pharmacological and nonpharmacological treatments on thyroid hormone metabolism and concentrations in rat brain. *Endocrinology*; 141: 1027-1040.
- Gittoes, N.J., & Franklyn, J.A. (1995). Drug-induced thyroid disorders. *Drug Saf*; 13: 46-55.
- Gründer, G., Wetzel, H., Schlösser, R., Angheliescu, I., Hillert, A., Lange, K., *et al.*, (1999). Neuroendocrine response to antipsychotics: Effects of drug type and gender. *Biol Psychiatry*; 45: 89-97.
- Jefferson, J.W. (1988). Halldol decanoate and thyroid disease [letter]. *J Clin Psychiatry*; 49: 457-458.
- Kelly, D.L. and Conley, R.R. (2005). Thyroid function in treatment resistant schizophrenia patients treated with quetiapine, risperidone, or fluphenazine. *J Clin Psychiatry*; 66: 80-84.
- Kline, N. S., Blair, J., Cooper, T. B., Esser, A. H., Hackett, E., Vestergaard, P. (1968). A controlled seven year study of endocrine and other indices in drug treated chronic schizophrenics. *Acta Psychiatr Scand. Suppl*; 206: 7-75.
- Kundra, P. and Burman, K.D. (2012). The effects of medications on thyroid function test. *Med Clin North Am*. 96: 283-295.
- Linnet, K. (2002). Glucuronidation of olanzapine by cDNA-expressed human URP-glucuronosyltransferases and human liver microsomes. *Hum Psychopharmacol*; 17: 233-238.
- MacDonald, A.W. and Schulz, S.C. (2009). "What we know: findings that every theory of Schizophrenia should explain," *Schizophrenia Bulletin*; 35: 493-508.
- Paunovic, V.R., Timotijevic, T., and Markinkovic, D. (1991). Neuroleptic actions on the thyroid axis; different effects of clozapine and haloperidol. *Int Clin Psychopharmacol*; 63:133-139.
- Anonymous Physician's Desk Reference PDR. (2003). 56th ed. Montvale. NJ: Medical Economics Co. Inc; 667-673.
- Sim, K., Chong, S.A., Chan, Y.H., and Lum, W.M. (2002). Thyroid dysfunction in chronic schizophrenia within a state psychiatric hospital. *Ann Acad Med Singapore*; 31: 641-644.
- Singer, P.A. (1986). Thyroid function tests and effects of drugs on thyroid function. In: Lavin N, ed. *Manual of Endocrinology and Metabolism*. Boston, Mass: Little, Brown and Company; 341-354.
- Vansell, N.R., Klaassen, C.D. (2002). Effect of microsomal enzyme inducers on the biliary excretion of triiodothyronin (T3) and its metabolites. *Toxicol Sci*; 65: 184-191.